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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,146	01/17/2002	Bernhard Hauer	50915	6323

26474 7590 11/24/2010

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
11/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,146	HAUER ET AL.	
	Examiner	Art Unit	
	YONG D. PAK	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,30-35,37,50 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,30-35,37,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP00/07253.

The amendment filed on September 13, 2010, amending claims 27-28, 30-35, and 37, canceling claims 29, 36, and 38-49, and adding claims 50-51, has been entered.

Claims 27-28, 30-35, 37, and 50-51 are pending and are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on September 13, 2010, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

In view of the amendment of claims 27 and 36, the objection to claims 27 and 36 has been **withdrawn.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28, 30-35, 37, and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 27-28, 30-35, 37, and 50-51 are drawn to a method for the oxidation of a substrate compound having an N-, O- or S-heterocyclic mono-or polynucleoear aromatic moiety or a method for the microbiological production of indigo and/or indirubin by incubating an indole-containing reaction medium with a monooxygenase derived from cytochrome P450 monooxygenase BM-3 from Bacillus megaterium having the amino acid of SEQ ID NO:2 by mutation and the monooxygenase has a functional mutation which consists of a mutation in at least one of sequence positions 74, 87, and 188. It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." The term "has" in transitional phrases does not create a presumption that the body of the claim is closed (See MPEP 2111.03). Therefore, the examiner has broadly interpreted the phrase "the monooxygenase has a functional mutation which consists of a mutation in at least one of sequence positions 74, 87, and 188" as a mutant monooxygenase derived from SEQ ID NO:1 by mutation of the recited regions and any other mutations in any other positions. The limitation "has a functional mutation which consists of a mutation in at least one of sequence positions 74, 87, and 188" provides no description on the

structure of other parts of the enzyme. Thus the claims encompass a method of using any variants, mutants and recombinants of SEQ ID NO:2 comprising any number of mutations at the recited positions and in other positions. Therefore, the claims are drawn to a method of using a genus of monooxygenase having unknown structure.

In *University of Calfornia v. Eli Lilly & Co.,* 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The recitation of "monooxygenase" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus

without providing any definition of the structural features of the species within the genus. The CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "monooxygenase" proteins used in the claimed method, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

The claims are drawn to a method of using a genus of monooxygenases having uknown structure. The specification only describes a method for oxidizing indoles with a modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein said modified cytochrome P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188GIn and Ala74Gly. While MPEP 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by

disclosing only one species within the genus." In view of the widely variant species encompassed by the genus, these few examples of a single species of a specific mutant of SEQ ID NO:2 is not enough and does not constitute a representative number of species to describe the whole genus of any or all variants, recombinant and mutants of SEQ ID NO:2 comprising an amino acid substitution at position(s) 74, 87, and/or 188 and any other mutations at any other positions, and there is no evidence on the record of the relationship between the structure of the monooxygenase of SEQ ID NO:2 and the structure of any or all variants, recombinant and mutants of SEQ ID NO:2. Therefore, the specification fails to describe a representative species of the genus comprising monooxygenase having unknown structure.

Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants should note that the rejection has been amended in light of the amendment of the claims.

Claims 27-28, 30-35, 37, and 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for oxidizing indoles with a modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the modified P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188GIn and/or Ala74Gly, does not reasonably provide enablement for a method for oxidizing indoles with a modified cytochrome P450 monooxygenase having unknown structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 27-28, 30-35, 37, and 50-51 are drawn to a method for the oxidation of a substrate compound having an N-, O- or S-heterocyclic mono-or polynucleoear aromatic moiety or a method for the microbiological production of indigo and/or indirubin by incubating an indole-containing reaction medium with a monooxygenase derived from cytochrome P450 monooxygenase BM-3 from Bacillus megaterium having the amino acid of SEQ ID NO:2 by mutation and the monooxygenase has a functional

mutation which consists of a mutation in at least one of sequence positions 74, 87, and 188.

The breadth of the claims.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." The term "has" in transitional phrases does not create a presumption that the body of the claim is closed (See MPEP 2111.03). Therefore, the examiner has broadly interpreted the phrase "the monooxygenase has a functional mutation which consists of a mutation in at least one of sequence positions 74, 87, and 188" as a mutant monooxygenase derived from SEQ ID NO:1 by mutation of the recited regions and any other mutations in any other positions. The limitation "has a functional mutation which consists of a mutation in at least one of sequence positions 74, 87, and 188" provides no description on the structure of other parts of the enzyme. Thus the claims encompass a method of using any variants, mutants and recombinants of SEQ ID NO:2 comprising any number of mutations at the recited positions and in other positions. Therefore, the claims are drawn to a method of using a monooxygenase having unknown structure. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of serine proteases isolated from any or all source, including any or all mutants, recombinants and variants thereof. In the instant case, the specification enables only a method for oxidizing indoles with a modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the modified

P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188GIn and/or Ala74Gly.

The state of prior art, the relative skill of those in the art, and predictability or unpredictability of the art.

Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within a cytochrome P450 monooxygenase can be modified and which ones are conserved such that one of skill in the art can make the recited polypeptides having cytochrome P450 monooxygenase activity, (2) which segments of SEQ ID NO:2 are essential for activity, and (3) the general tolerance of cytochrome P450 monooxygenase to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991)

teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions.

The amount of direction or guidance presented and the existence of working examples.

The specification discloses a method for oxidizing indoles with a modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the modified P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188Gln and/or Ala74Gly. However, the speciation fails to provide any information as to (1) specific substrates associated with any cytochrome P450 monooxygenase isolated from any source, including variants, mutants and recombinants thereof, (2) structural elements required in a polypeptide having cytochrome P450 monooxygenase activity, or (3) which are the structural elements in a cytochrome P450 monooxygenase that are essential to display cytochrome P450 monooxygenase activity. No correlation between structure and function of having cytochrome P450 monooxygenase activity has been presented. There is no information or guidance as to which amino acid residues in any cytochrome P450 monooxygenase can be modified and which ones are to be conserved to create a polypeptide displaying cytochrome P450 monooxygenase activity.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.

While enzyme isolation techniques, recombinant and mutagenesis techniques were known in the art at the time of the invention, e.g. hybridization or mutagenesis, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, it is not routine in the art to create variants of polynucleotides encoding polypeptides having the activity recited without any knowledge as to the structural features which would correlate with that activity.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability of the prior art in regard to structural changes and their effect on function and the lack of knowledge about a correlation between structure and function, an undue experimentation would be necessary one having ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance,

determination of polypeptides having the desired biological characteristics recited in the claims are unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants should note that the rejection has been amended in light of the amendment of the claims.

Claim Rejections - 35 USC § 102

In view of applicant's arguments, the rejection of claims 27-37 under 35 U.S.C. 102(b) as being anticipated by Graham-Lorence et al. has been withdrawn.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652